

A hypothesis on biological protection from space radiation through the use of new therapeutic gases as medical counter measures

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ABSTRACT

Radiation exposure to astronauts could be a significant obstacle for long duration manned space exploration because of current uncertainties regarding the extent of biological effects. Furthermore, concepts for protective shielding also pose a technically challenging issue due to the nature of cosmic radiation and current mass and power constraints with modern exploration technology. The concern regarding exposure to cosmic radiation is the biological damage it induces. As damage is associated with increased oxidative stress, it is important and would be enabling to mitigate and/or prevent oxidative stress prior to the development of clinical symptoms and disease. This paper hypothesizes a “systems biology” approach in which a combination of chemical and biological mitigation techniques are used conjunctively. It proposes using new, therapeutic, medical gases as both chemical radioprotectors for radical scavenging and biological signaling molecules for management of the body’s response to exposure. From reviewing radiochemistry of water, biological effects of CO, H₂, NO, and H₂S gas, and mechanisms of radiation biology, it is concluded that this approach may have great therapeutic potential for radiation exposure. Furthermore, it also appears to have similar potential for curtailing the pathogenesis of other diseases in which oxidative stress has been implicated including cardiovascular disease, cancer, chronic inflammatory disease, hypertension, ischemia/reperfusion injury, acute respiratory distress syndrome, Parkinson’s and Alzheimer’s disease, cataracts, and aging.

Keywords: space radiation, radiolysis, radiochemistry, radiation shielding, therapeutic medical gas, reactive oxygen species, oxidative stress, countermeasure

REVIEW

The Challenge of Space Radiation

Galactic Cosmic Rays (GCR), solar energetic particles (SEP), and trapped energetic particles in a planetary magnetic field are natural sources of radiation in space. GCRs consist of highly energetic nuclei, predominately protons and He, but also with trace amounts of C, O, Ne, Si, Ca, and Fe ions. Particle energies can range from 100 MeV to 10 GeV per nucleon. Although the high charge and energy (HZE) nuclei are in trace amounts, they are still of concern because they can cause more damage than protons since they are more highly ionizing. As well, even though particle fluencies are typically low, they are chronic and can significantly increase with solar events. Furthermore, GCRs and SEPs impinging on shielding material, atmosphere, or surface of a planet or satellite can produce secondary radiation, including energetic neutrons, from nuclear fragmentation of the primary ion and target atoms. This can introduce an additional component to the radiation field which makes shielding from HZE quite challenging and poses one of the principal unknowns in understanding the effects of HZE effects with human tissue [1]. Furthermore, while our bodies do possess a natural repair mechanism, radiation with a high linear energy transfer (LET) rate, like space radiation, is attributed to be more likely to cause double strand breaks in DNA that are relatively more difficult for our natural repair mechanisms to fix correctly [2]. While a week or month of this radiation at the dose rates naturally present likely will not have serious consequences, several year durations in space could.

The traditional paradigm for radiation protection is to minimize exposure time, maximize distance from radiation sources, and use shielding to attenuate and absorb radiation before it can deposit its energy in humans. In regards to minimizing exposure time, new propulsive technologies could reduce trip times but have yet to be developed and would not address the ability to remain at a location for long durations. It is impractical to maximize distance from cosmic radiation sources. In regards to shielding, aspects of attenuation by mass or deflection by magnetic fields or charge repulsion have been considered. Due to the phenomena of secondary radiation, shielding by other matter may require a significant amount of mass which could be impractical within current mass constraints in space systems. Due to the high energy of the space radiation, magnetic field and charge strengths required may be unreasonable due to current mass and power constraints in space systems along with other system design

implications. In short, shielding space radiation is seemingly quite challenging. However, advances in biochemistry may reveal some more tools for radiation protection [1].

Parallels between Radiation Biology & Chemistry of Water

Radiolysis is the decomposition of water from exposure to ionizing radiation. Radiation chemistry of water has been well studied since the onset of nuclear power production, as water has been the most often used coolant. Since mammalian cells are composed of about 80% water, it seemed natural that there exist similarities between radiation chemistry of water and radiation biology. It is these similarities from which analogues for radioprotective measures were inspired.

Chain of Events Initiated by Chemically Reactive Species

Radiolysis in nuclear systems causes a chain of events that ultimately manifest into systematic problems like corrosion and gas generation. Ionizing radiation creates chemically reactive radicals H_3O^+ , e^- , H^+ , H , and OH by ionizing and/or breaking the bonds of water molecules. These radicals then initiate a chain of chemical reactions within the water which can result in the formation of molecular decomposition products such as H_2 , O_2 , HO_2 and H_2O_2 [3]. These oxidizing species alter the water composition and therefore its electrochemical character which facilitates the manifestation of problems like corrosion or gas generation. As such, the nature in which systematic problems develop can be viewed as stemming from a chain of events that are initiated by ionization and propagated by a scheme of chemical reactions depending upon the net result of the ensuing chemistry.

This situation is similar in nature to a biological system and the pathogenesis of radiation related ailments. Ionization of key biological molecules can lead to chemical reactions which transform these molecules. This alters their biochemical function and can result in changes of cellular properties. This propagates from tissue to organ to system changes that ultimately manifest into clinical symptoms and ailments. Ionization of the molecules can occur both directly by radiation and indirectly by free radicals and reactive oxygen species (ROS) created by radiolysis. Free radicals and ROS like O_2^- , ${}^1\text{O}_2$, $\cdot\text{OH}$, $\cdot\text{OOH}$, $\text{NO}\cdot$ and H_2O_2 can cause cell injury or death by oxidative stress [4,5]. Oxidative stress can result in DNA damage, lipid peroxidation and also lead to a loss of protein after reductive remodeling of skeletal muscle due to undernutrition in space [6]. Radiation-induced damage of chromosomes in lymphocytes may compromise the immune system's ability to prevent tumor development [7]. In

general, the greatest risks from exposure are assumed to be cancer, cataracts, [8] and damage to the central nervous system [9]. Interestingly enough, oxidative stress has been implicated to play a role in the development of other diseases [10,11] including cardiovascular disease, cancer [12], chronic inflammatory disease [13], hypertension [14], ischemia/reperfusion injury [4], acute respiratory distress syndrome (ARDS) [15], neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease [16,17] and aging [18]. Certain detrimental effects from space radiation on the dopaminergic system are similar to functional changes that occur from Parkinson's disease [9], diabetogenic problems associated with increased C-peptide excretion and insulin resistance [19], as well as constipation due to malfunction of intestine. That is, the normal production and development of these disorders and diseases have also been associated with an increase of oxidative stress and inflammation similar to that which would likely be caused or increased by exposure to space radiation. Thus the nature of the problem seems similar to nuclear systems in that systematic manifestations result from a chain of events initiated by ionization and propagated, in this case, by ensuing chemical reactions and biological responses.

Radical Scavenging & Antioxidants

The actual chemical reactions that ensue and their by-products depend upon what the radicals come into contact with. For example, in pure water, radical-radical interactions lead to the formation of the decomposition products while radical-decomposition product reactions lead to the reformation of water. In a nuclear system, manifestation of system level problems has been curtailed by interfering with the chain of events early on during the chemical stages through the use of additives that alter water composition. Whereas some additives have been found to promote and increase water decomposition, others have been found to suppress it [20]. This occurs through scavenging in which the additives preferentially react with the radicals. Scavenging has the effect of removing reactive species from the system and thereby reduces their ability to participate in chemical reactions that cause decomposition. While there are various additives that preferentially react with decomposition products, the byproducts of the scavenging reaction are a factor as they are part of the composition. For example, some ionic impurities scavenge radicals but do so at the expense of the water reformation process as the consumed radicals are no longer available to react with decomposition products in the chemical reactions that lead to water reformation as shown in 1-4.





However, the use of hydrogen as a scavenger produces byproducts that promote the water reformation process while neutralizing radicals.



The ability of H_2 to suppress total oxidant concentrations in a water system exposed to radiation has long been recognized by the boiling water reactor (BWR) community and is referred to as hydrogen water chemistry (HWC). The addition of H_2 to water has the effect of suppressing the Open Circuit Potential (OCP) of the water (Figure 1) thereby electrochemically reducing the driving potential for corrosion.

FIGURE 1. The Effect on OCP of the Solution From H_2 Gas Bubbled Into it and the Addition of 0.1 M H_2O_2 as Measured by Tungsten/Tungsten-Oxide (ref. electrode) and Platinum Electrodes (vs. Saturated Calomel Electrode SCE) [21].

In a biological system, antioxidants have been seen to protect against oxidative stress and prevent the pathological process of a wide range of disease [22]. The effect of antioxidants in reducing oxidative stress can be attributed to their ability to protect tissues from free radicals [5] hinting towards a scavenging mechanism. Turner [23] indicates, “A number of radiosensitizing chemicals and drugs are known. Some sensitize hypoxic cells, but have little or no effect on normally aerated cells. Other agents act as radioprotectors reducing biological effectiveness...which scavenge free radicals. Still other chemicals modifiers have little effect on cell killing but substantially enhance some multistep processes, such as oncogenic cell transformation.” Thus it appears that radical scavengers or antioxidants act as radioprotectors that chemically protect against indirect ionization by preferentially reacting with the reactive species thus reducing their ability to cause oxidative stress.

This dependency of outcome on scavenger type is similar to nuclear systems where the effect of the additive can either be to promote water decomposition or water reformation. One such example is the effect of oxygen. There appear to be parallels in the effect of oxygen to promote water decomposition in a nuclear system and increased radiosensitivity of cells in the presence of oxygen as shown in Figure 2C. Figure 2D also includes the effect of

hydrogen and shows that when in excess of ROS like O_2 and H_2O_2 , the water reformation process dominates as ROS are quickly scavenged. This begs the question of what the effect of H_2 would be on radiosensitivity. Also noteworthy in figure 2 is the occurrence of an equilibrium where the amount of molecular decomposition byproducts from radiolysis remains constant. This reflects a balance between water decomposition and reformation process and hints at the ability for radical scavengers to affect which process dominates. Biological parallels and implications of this are discussed next.

FIGURE 2. (A)-(D) [24] Reflect Water Decomposition by the Concentration of Radiolysis byproducts. (B) is an Extension of (A) and is Air Free Pure Water. Decomposition Ensues until H_2 in Excess of ROS. (C) is Effect of Dissolved O_2 in Excess of H_2 to Promote Decomposition. (D) is Effect of Dissolved Hydrogen in Excess of O_2 to Scavenge. (E) [23] Shows Effect of O_2 as a Biological Radiosensitizer. N_2 is Also Shown Which Begs the Question of the Effect of H_2 .

The Net Effect of Competing Processes & Natural Repair Mechanisms

Radiolysis of water results in chemical reactions that are part of two competing processes: decomposition and reformation. Decomposition will still occur even in the presence of additives but they serve to alter the net effect by affecting the chemical reactions such that one process becomes more dominate. This was seen somewhat in figure 2 and is shown more explicitly in figure 3 which shows that the threshold for which negative effects can manifest can be increased through bolstering the scavenging capacity and altering the balance so that the favorable processes are dominant.

FIGURE 3. Relative Contribution of the Water Decomposition Process is Associated with Boric Acid Concentration Measured in Milli-molar on the Abscissa. System Scavenging Capacity or Relative Contribution of the Water Reformation Process is Associated with the Initial Amount of Dissolved H_2 Measured in Micro-molar Concentrations (each curve). Manifestation of Negative Systematic Effects is Reflected by the Amount of Water Decomposition from Radiolysis as Reflected by H_2 Gas Generation Rates Measured in Micro-molar Concentrations per Minute on the Ordinate. Figure Illustrates That the Addition of dissolved H_2 Increases the Scavenging Capacity of the Water Therefore Increasing the Threshold and Delaying the Onset of when Decomposition Becomes the Dominant Process [27].

As mentioned earlier, free radicals and ROS were identified as the root cause of oxidative stress in a biological system. While free radicals and ROS are created from exposure to external sources like X-rays, ozone, cigarette smoke, air pollutants and industrial chemicals [25], they also are naturally generated during a variety of energy-generating biochemical reactions and cellular functions [4]. Furthermore, the ROS actually serve a necessary function as signaling molecules that critically modulate the activation of the immune system and thus participate in antibacterial defense [26]. Oxidative stress occurs when there is an imbalance between antioxidants and ROS and free radicals [28] such as when radiation exposure increases the amount of free radicals and ROS through production by ionization. Thus, in the biological system, it similarly appears to be a situation of competing processes between biochemical damage and repair processes. Chopping observes, “The cell is protected by different DNA repair mechanisms which try to restore the damage. We don’t know the details, except when the repair goes wrong (e.g. a replacement of a lost nucleotide by a ‘wrong’ base pair, etc.)... The cell contains natural radical scavengers. As long as they are in excess of the radiolysis products, the DNA may be protected. When the products exceed the amount of scavengers, radiation damage and cancer induction may occur. In principle, there could thus be a threshold dose for radiation damage, at which the free radicals formed exceed the capacity of scavenging. The scavenging capacity may differ from individual to individual depending on his/her physical condition” [2]. Experimental investigations regarding long-duration space flights in particular clearly showed increased oxidative stress markers and a reduction in antioxidants after these flights [29, 6]. Kennedy et al. demonstrated that exposure to space radiation may compromise the capacity of the host antioxidant defense system and that this adverse biological effect can be prevented, at least partially, by dietary supplementation with agents expected to have effects on antioxidant activities [30]. Interestingly and similarly so, the radiation resistance of the bacteria *Deinococcus radiodurans* that can grow under chronic γ radiation (50 Gy/hr) or recover from acute doses greater than 10 kGy has been attributed to the role of antioxidants in mitigating the extent of oxidative damage [31-33]. Thus there appear to be similarities between the nuclear and biological systems in how use of scavengers can enhance and bolster the favorable process thereby increasing the natural radiation resistance of the system. Thus, we hypothesize a strategy that (1) interrupts the chain of events leading to biological disease and (2) bolsters natural repair processes and reduces damage processes could have a great effect on increasing the threshold after which radiation damage propagates to the systematic symptoms.

Radiation protection by a biochemical conjunctive approach

Over the course of the last century, a wealth of knowledge has been accumulated on the effect of radiation on biological systems. Areas spanning in scope from DNA damage up to changes in physiology have received extensive study. To date, biology studies of radiation damage have largely focused on components of DNA repair systems such ataxia telangiectasia mutated gene (ATM). More recently, however, it has been found that modification of key molecular targets can protect tissue from radiation induced fibrosis in mice exposed to doses up to 25Gy [34,35]. It has also been found that changes in APOE (Apolipoprotein E) genotype dramatically influences survival following Total Body Irradiation (TBI) in murine models. These results imply that modification of key molecular targets to induce biological changes in the host can protect tissue from radiation damage. We suggest the use of new therapeutic medical gases to administer radioprotectors and biological signaling molecules to work conjunctively in preventing, protecting, and repairing radiation damage. Turner notes that, “for carcinogenesis or transformation, for example, such biological promoters (radioprotectors) can dwarf the effects of physical factors, such as LET and dose rate, on dose-response relationships” [23].

Radioprotectors have been implicated to work by the following chemical and biological mechanisms:

1. radical scavenging of toxic decomposition products of free radicals and ROS
2. repair of biological molecules by donation of H atoms since hydrogen bonds are among the weakest in biological molecules and such are the first to be broken [36]
3. interaction with cellular components (binding, altering metabolic pathway, etc.)

Interaction with cellular components can have biological effects that lend to radioprotection like hypoxia, alteration of metabolic state, and anti-apoptotic properties. Tissue hypoxia decreases the radiosensitivity of cells by minimizing the O₂ effect and can be produced chemically by impairing oxygen transport (binding up hemoglobin with another molecule) or biologically by restricting blood flow (vasoconstrictor drug) or lowering blood pressure (vasodilator drug). Inducing a hypometabolic state which resembles hibernation, may contribute to tolerance against oxidative stress. Metabolic rates in hibernating marmots and ground squirrels help delay the onset of obvious damage. Also, survival times for guinea pigs that have received massive doses of radiation (>6000 rads) have been extended from several hours to about 4 days through the use of central nervous system depressants

(pentobarbital) where it has been attributed to partial protection from central nervous system syndrome [36]. Furthermore, a hypometabolic status may also prove to be an ideal therapy for various shock or trauma states in which dramatic reduction in metabolic demands may be highly protective [37]. Anti-apoptotic properties can mitigate organ damage such as in IR injury by reducing the amount of cellular self destruction. Interference with mitosis and DNA synthesis can slow cells in their radio-resistant phase of cell division and afford more time for natural repair of the cell prior to replication of the damage. NO, CO, H₂S and H₂ are gaseous signaling molecules in humans. These molecules act as transmitters of information between cells by chemically interacting with cell receptors to trigger a response within the cell. These comprise some of the medical gases of interest and many of them act both on the chemical level in the form of antioxidant radical scavenging and on the biological level in the form anti-inflammatory, anti-apoptotic, and other biological effects. Extensive and more detailed information about these gases in a therapeutic role can be found in [22] which provides a detailed description of medical gases of interest and their properties and [38] provides detailed information pertaining in particular to H₂.

Hydrogen

Hydrogen has only recently been considered for therapeutic applications for radiation exposure [39, 40] and recent results have demonstrated its radioprotective effects in cultured cells and mice [41]. Hydrogen properties as a medical gas are summarized in Table 1. Hydrogen may have potential as a safe and potent therapeutic medical gas, as well as several potential advantages over current pharmacological therapies for the following reasons:

- It is highly diffusible and as such could potentially reach subcellular compartments, such as mitochondria and nuclei, which are the primary site of ROS generation and DNA damage [42] and are also notoriously difficult to target pharmacologically.
- Its hyporeactivity with other gases at therapeutic concentrations may allow hydrogen to be administered with other therapeutic gases, including inhaled anaesthesia agents [43].
- H₂ may spare the innate immune system while still allowing phagocytosis of infecting organisms. When tested *in vitro*, it did not eliminate O₂⁻ or H₂O₂ which have important functions in neutrophils and macrophages as they must generate ROS in order to kill some types of bacteria engulfed by phagocytosis [42]. It is not clear whether a similar reaction preferentially occurs under complex biological conditions.

Experimental studies have demonstrated that hydrogen has potent therapeutic efficacies on both parasite infection [44] and polymicrobial sepsis [45].

- No adverse effects have been found in humans drinking hydrogen water in a study that examined the effects of drinking hydrogen-rich water (HW) for radiation-induced late adverse effects [46, 47]. Studies showed that the consumption of HW for 6 months resulted in significant decrease of serum levels of derivatives of Reactive Oxidative Metabolites (dROMs) and an increase of biological antioxidant power determined by Free Radical Analytical System (FRAS). No severe adverse effects were seen during follow up period. These results suggest that drinking HW improved Quality of Life (QOL), associated with decrease of oxidative injury markers, in patients with radiotherapy.

Nitric Oxide

Medical properties for NO are summarized in Table 2 and effects are shown in Figure 4. NO regulates platelet activity, preservation of the normal structure of the vessel wall and causes blood vessel dilation which may increase tissue blood supply [22]. This could abate inflammatory response and thus protect tissue from oxidative injury. It also may enhance the natural repair as mechanism as it is believed to be more effective in a living organism, where the cells are in continuous exchange with the surrounding cells and body fluids, than in the tissue samples often studied in the laboratory [2]. Results from NO studies that have examined the ability of patients to inhale NO to improve outcome of acute respiratory distress syndrome (ARDS) have had discrepant results from positive, negative or neutral outcomes. Thus NO may be linked with both protective and toxic effects depending upon concentrations, source, timing of administration and the environment suggesting a narrow window for administration in the treatment of oxidative injuries [48]. Reduction of excessive and deleterious NO effects appear to be controlled by blocking NO/cGMP signaling through thrombospondin-1 signaling via its receptor CD47. This has shown to both maintain the viability of normal tissues against radiation induced fibrosis in murine models following total body irradiation (25 Gy) and increase the radiosensitivity of tumors [34, 49, 35].

FIGURE 4. Images Compare Treated and Untreated Hind Limbs 8 Weeks After An Exposure of 25 Gy Showing That Signs of Fibrotic Contractures Occurred Only in the Untreated Limb [49].

Carbon Monoxide

Table 3 summarizes medical properties of CO gas. While the adverse effects of inhaled CO are a major concern for clinical use, experimental models have demonstrated that potent therapeutic efficacies exist at low concentrations [22, 50]. Soluble forms of CO, such as CO-releasing molecules, may overcome the problem of tissue hypoxia and allow clinical application [51, 52]. Recent animal studies have shown discrepant results between exhibiting and not exhibiting anti-inflammatory effects [22]. These discrepancies may be attributed to species specific differences in the affinity of CO for hemoglobin, or physiological differences such as respiratory rate and sensitivity to lipopolysaccharides (endotoxins) [53, 54]. Figure 5 shows that administration of H₂/CO mixtures has been shown to reduce structural damage to hearts in Lewis rats undergoing heart transplantation (HTx) in which oxidative stress injury is caused by ischemia/reperfusion [22] rather than radiation exposure.

FIGURE 5. Extent of Gross Structural Damage to Heart Graft Was Evaluated by TTC staining 3 h After Reperfusion. H₂ and CO Inhalation Reduced Ischemic Area Following Heart Grafts but with Only Slight Significance. Significant Reduction is Seen by Dual Treatment [22].

Hydrogen Sulfide

H₂S is produced enzymatically at micromolar levels in mammals and is believed to help regulate body temperature and metabolic activity at physiological concentrations [55, 56]. It has been implicated as the mechanism by which consumption of garlic attenuated cardiovascular disease where production of the gas has been demonstrated to occur by bioconversion of garlic-derived polysulfides by red blood cells [56]. According to Lefer [37], it appears that H₂S possesses all of the positive effects of NO without the capacity to form the toxic metabolite such as ONOO⁻. The medical properties of H₂S are summarized in Table 4.

Possible administration methods

Hydrogen or combinations of other medical gases could be administered to astronauts by inhalation, ingestion or injection. Inhalation could be achieved through a ventilator circuit, facemask, nasal cannula, or creating a spacesuit or spacecraft atmosphere which is composed of or contains a non-flammable gas mixture of these therapeutic

medical gases. The use of Hydreliox, an exotic breathing gas mixture of 49% hydrogen, 50% helium and 1% oxygen for prevention of decompression sickness and nitrogen narcosis during very deep technical diving [57] is one example of human inhalation of hydrogen gas mixtures. Drinking hydrogen-rich water (HW) appears to have comparable effects to hydrogen inhalation [58]. Although inhaled hydrogen gas may act more rapidly, oral intake of hydrogen-rich water is another method which may be more practical for daily life or suitable for continuous consumption in preventive or therapeutic uses. Ingestion of gas dissolved solutions may prove to be more portable, easily administered, and a safe means of delivering molecular hydrogen [59]. Gas rich water in which the gases have been dissolved could be prepared by bubbling gases into solution under pressure or other dissolution methods like swept gas diffusion. However, consideration will have to be given to loss of gas over time by dissolution and diffusion. Alternatively, some therapeutic gases such as hydrogen could be generated in solution by chemical reaction with the solution such as magnesium ($Mg + 2H_2O \rightarrow Mg(OH)_2 + H_2$). In this case for example, a magnesium stick could be inserted into the water just prior to drinking. However, consideration will also have to be given to ingestion of other produced byproducts. Though oral administration is safe and convenient, hydrogen can be lost from solution by dissolution and diffusion and some hydrogen is lost in the stomach or intestine, making it difficult to control the concentration of hydrogen administrated. Administration of hydrogen via an injectable hydrogen-rich solution may allow delivery of more accurate concentrations of hydrogen [60]. This method of administration has been demonstrated for hydrogen in mice [41].

CONCLUSIONS

We hypothesize a systems approach of using various therapeutic medical gases as chemical radioprotectors in conjunction with biological signaling molecules to disrupt the chain of events initiated by radiation exposure and interfere with pathogenesis of disease. This could have a profound positive effect as it addresses prevention, protection, and repair. This represents a novel and feasible preventative/therapeutic strategy to address radiation-induced adverse events and thus the challenge of space radiation. While more studies are warranted to apply this therapy for space travel and determine details of optimum gas mixtures and therapy administration plans, it appears that it represents a potentially novel, therapeutic, and preventative strategy that may also ameliorate symptoms for other oxidative stress related diseases as has been shown in relevant ground-based (animal) models.

LIST OF ABBREVIATIONS

APOE	Apolipoprotein E
ARDS	Acute Respiratory Distress Syndrom
ATM	ataxia telangiectasia mutated gene
BWR	Boiling Water Reactor
DNA	Deoxyribonucleic acid
dROMS	derivatives of Reactive Oxidative Metabolites
FRAS	Free Radical Analytical System
GCR	Galactic Cosmic Rays
Gy	Grey
HTx	Heart Transplantation
HW	Hydrogen Water
HWC	Hydrogen Water Chemistry
HZE	High Z and Energy (Z - Atomic #)
LET	Linear Energy Transfer
OCP	Open Circuit Potential
QOL	Quality of Life
ROS	Reactive Oxygen Specie
SEP	Solar Energetic Particles
TBI	Total Body Irradiation

COMPETING INTERESTS

The authors declare they have no competing interest.

AUTHOR'S CONTRIBUTIONS

MS developed the concept of using Hydrogen as a radioprotectant by noting parallels between radiation chemistry of water and radiation biology and conducting the literature review in these areas as well as the compilation of this paper. RA provided review of the concept and provided information regarding oxidative stress from space travel and advanced methods of diagnostics. AN provided review of the concept and provided information and references regarding therapeutic uses of medical gases. DW provided review of the concept and provided information regarding NO.

AUTHOR'S INFORMATION

Any opinions expressed are those of the authors and do not necessarily reflect the views of NASA.

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REFERENCES

1. Parker, EN: **Shielding Space Travelers.** *Scientific American*, March 2006, pp. 40-47.
2. Chopping G, Liljenzin J, Rydberg J: **Radiation Biology and Radiation Protection.** In *Radiochemistry and Nuclear Chemistry*. 3rd edition. Butterworth-Heinemann; 2002:474-513.
3. Lin C: **Radiation Chemistry in Reactor Coolant.** In *Radiochemistry in Nuclear Power Reactors*. Washington, DC: National Academy Press; 1996:125-142.
4. Nakao A, Kaczorowski DJ, Sugimoto R, Billiar TR, and McCurry, KR: **Application of heme oxygenase-1, carbon monoxide and biliverdin for the prevention of intestinal ischemia/reperfusion injury.** *J. Clin. Biochem. Nutr.* 2008, **42**:78-88.
5. Hanaoka K: **Antioxidant Effects of Water Produced by Electrolysis of Sodium Chloride Solutions.** *Journal of Applied Electrochemistry* 2001, **31**:1307-1313.
6. Stein TP: **Space Flight and Oxidative Stress.** *Nutrition* 2002, **18**:867-871.
7. Testard I, Ricoul M, Hoffschir F, Flury-Herard A, Dutrillaux B, Fedorenko B, Gerasimenko V, Sabatier L: **Radiation-induced Chromosome Damage in Astronauts' Lymphocytes.** *Int. J. Radiat. Biol.* 1996, **70**:403-411.
8. Barr YR, Bacal K, Jones JA, Hamilton DR: **Breast Cancer and Spaceflight: Risk and Management.** *Aviat Space Environ Med* 2007, **78**:A26-37.
9. Koike Y, Frey MA, Sahiar F, Dodge R, Mohler S: **Effects of HZE Particle on the Nigrostriatal Dopaminergic System in a Future Mars Mission.** *Acta Astronaut* 2005, **56**:367-378.
10. Packer L, Fuchs JJ: *Vitamin C in Health and Disease*. New York: Marcel Dekker; 1997.
11. Sohal RS, Weindurch R: **Oxidative Stress, Caloric Restriction, and Aging.** *Science* 1996, **273**:59-63.
12. Cerutti PA, Trump BF: **Inflammation and oxidative stress in carcinogenesis.** *Cancer Cells* 1991, **3**:1-7.
13. Ha H, Park J, Kim YS, Endou H: **Oxidative stress and chronic allograft nephropathy.** *Yonsei. Med. J.* 2004, **45**:1049-1052.
14. Watson T, Goon PK, Lip GY: **Endothelial Progenitor Cells, Endothelial Dysfunction, Inflammation, and Oxidative Stress in Hypertension.** *Antioxid. Redox Signal.* 2008, **10**:1079-1788.
15. Tasaka S, Amaya F, Hashimoto S, Ishizaka A: **Roles of oxidants and redox signaling in the pathogenesis of acute respiratory distress syndrome.** *Antioxid. Redox Signal.* 2008, **10**:739-753.
16. Nunomura A, Moreira PI, Takeda A, Smith MA, Perry G: **Oxidative RNA damage and neurodegeneration.** *Curr. Med. Chem.* 2007, **14**:2968-2975.

17. Loh KP, Huang, SH, De Silva, R, Tan, BK, Zhu, YZ: **Oxidative stress: apoptosis in neuronal injury** *Curr. Alzheimer. Res.* 2006, **3**:327–337.
18. Wei YH, Lu CY, Wei CY, Ma YS, Lee, HC: **Oxidative stress in human aging and mitochondrial disease consequences of defective mitochondrial respiration and impaired antioxidant enzyme system.** *Chin. J. Physiol.* 2001, **44**:1-11.
19. Tobin BW, Uchakin PN, Leeper-Woodford SK: **Insulin secretion and sensitivity in space flight: diabetogenic effects.** *Nutrition* 2002, **18**:842–8.
20. Schoenfeld MP: **A Review of Radiolysis Concerns for Water Shielding in Fission Surface Power Applications.** In *Proceedings of Space Technology and Applications International Forum 2008 (STAIF 2008)*. Edited by El-Genk M. New York: AIP Conference Proceedings 969; 2008:337-347.
21. Lillard RS, Pile DL, Butt DP: **The Corrosion of Materials in Water Irradiated by 800 MeV Protons.** *Journal of Nuclear Materials* 2000, **278**:277-289.
22. Nakao A, Sugimoto R, Billiar TR, McCurry KR: **Therapeutic Antioxidant Medical Gas.** *J. Clin. Biochem. Nutr.* 2009, **44**:1-13.
23. Turner JE: **Chemical and Biological Effects of Radiation.** In *Atoms, Radiation, and Radiation Protection*. 2nd edition. New York: John Wiley & Sons, Inc.; 1995:421-422.
24. Bjergbakke E, Draganic ZD, Sehested K, Draganic IG: **Radiolytic Products in Waters Part I: Computer Simulation of Some Radiolytic Processes in the Laboratory.** *Radioehimie Acta* 1989. **48**:65-71.
25. Dean RT: **Biochemistry and Pathology of Radical-Mediated Protein Oxidation.** *Biochem. J.* 1997. **324**:1-18.
26. Reth M: **Hydrogen peroxide as second messenger in lymphocyte activation.** *Nat. Immunol.* 2002. **3**:1129–1134.
27. Hart EJ, McDonell WR, Gordon S: **The Decomposition of Light and Heavy Water Boric Acid Solutions by Nuclear Reactor Radiations.** In *Proceedings of International Conference on the Peaceful Uses of Atomic Energy: 1955; Geneva*. New York: United Nations P/839; **7**:597.
28. Halliwell B, Gutteridge JM, Cross CE: **Free Radicals, Antioxidants, and Human Disease: Where are we Now?** *J. Lab. Clin. Med.* 1992. **119**:598-620.
29. Hollander J, Gore M, Fiebig R, Mazzeo R, Ohishi S, Ohno H, Ji L: **Spaceflight downregulates antioxidant defense systems in rat liver.** *Free Radic Biol Med* 1998. **24**:385–90.
30. Kennedy AR, Guan J, Ware JH: **Countermeasures against space radiation induced Oxidative Stress in Mice.** *Radiat Environ Biophys* 2007. **46**:201-203.
31. Daly MJ, Gaidamakova EK, Matrosova VY, Vasilenko A, Zhai M, Venkateswaran A, Hess M, Omelchenko MV, Kostandarites HM, Makarova KS, Wackett LP, Fredrickson JK, Ghosal D: **Accumulation of Mn(II) in *Deinococcus radiodurans* Facilitates Gamma Radiation Resistance.** *Scienceexpress* September 30, 2004.
32. Daly MJ, Gaidamakova EK, Matrosova VY, Vasilenko A, Zhai M, Leapman RD, Lai B, Ravel B, Li SW, Kemner KM, Fredrickson JK: **Protein Oxidation Implicated as the Primary Determinant of Bacterial Radioresistance.** *PLoS Biol.* 2007. **5**(4):0769-0779.
33. Ghosal D, Omelchenko MV, Gaidamakova EK, Matrosova VY, Vasilenko A, Venkateswaran, Zhai M, Kostandarites HM, Brim H, Makarova KS, Wackett LP, Fredrickson JK, Daly MJ: **How radiation Kills**

Cells: Survival of *Deinococcus radiodurans* and *Shewanella oneidensis* under Oxidative Stress. *FEMS Microbiology Reviews* 2005.

34. Isenberg JS, Maxhimer JB, Hyodo F, Pendra ML, Ridnour LA, DeGraff WG, Tsokos M, Wink DA, Roberts DD: **Thrombospondin-1 and CD47 Limit Cell and Tissue Survival of Radiation Injury.** *Am. J. Pathol.* 2008. **173**(4):1100-1112.
35. Maxhimer JB, Soto-Pantoja DR, Ridnour LA, Shih HB, DeGraff WG, Tsokos M, Wink DA, Isenberg JS, Roberts DD: **Radioprotection in Normal Tissue and Delayed Tumor Growth by Blockade of CD47 Signaling.** *Sci Transl Med.* 2009. **1**(3):3ra7.
36. Casarett AP: **Modification of Radiation Injury.** In *Radiation Biology*. New Jersey: Prentice-Hall, Inc.; 1968:249-262.
37. Lefer DJ: **A new gaseous signaling molecule emerges: Cardioprotective role of hydrogen sulfide.** In *Proceedings of the National Academy of Sciences*: November, 13, 2007; **104**(46):17907-17908.
38. Huang C, Kawamura T, Toyoda Y, Nakao A, **Recent Advances in Hydrogen Research as a Therapeutic Medical Gas.** *Free Radical Research* 2010. **44**(9):971-982.
39. Liu C, Cui, J, Sun, Q, Cai J: **Hydrogen Therapy may be an effective and specific Novel Treatment for Acute Radiation Syndrome.** *Medical Hypotheses*, 2009.
40. Schoenfeld MP, Ansari RR, Zakrajsek JF, Billiar TR, Toyoda Y, Wink DA, Nakao A: **Hydrogen therapy may reduce the risks related to radiation-induced oxidative stress in space flight.** *Med Hypotheses*, 2010.
41. Qian L, Cao F, Cui J, Huang Y, Zhou X, Liu S, Cai J: **Radioprotective effect of Hydrogen in Cultured Cells and Mice.** *Free Radical Research* 2010. **44**(3):275-282.
42. Ohsawa I, Masahiro I, Takahashi K, Watanabe M, Nishimaki K, Yamagata K, Katsura K, Katayama Y, Asoh S, Ohta S: **Hydrogen Acts as a Therapeutic Antioxidant by Selectively Reducing Cytotoxic Oxygen Radicals.** *Nat Med* 2007. **13**:688-694.
43. Nakao A, Kaczorowski DJ, Wang Y, Cardinal JS, Buchholz BM, Sugiimoto R, Tobita K, Lee S, Toyoda Y, Billiar TR, McCurry KR: **Amelioration of rat cardiac cold ischemia/reperfusion injury with inhaled hydrogen or carbon monoxide, or both.** *J Heart Lung Transplant* 2010. **29**:544-553.
44. Gharib B, Hanna S, Abdallahi, O, Lepidi H, Gardette B, De Reggi M: **Anti-inflammatory properties of molecular hydrogen: investigation on parasite-induced liver inflammation.** *C R Acad Sci* 2001. **3**:324:719-724.
45. Xie K, Yu Y, Pei Y, Hou L, Chen S, Xiong L, Wang G: **Protective Effects of Hydrogen Gas on Murine Polymicrobial Sepsis via Reducing Oxidative Stress and HMGB1 Release.** *Shock* 2009.
46. Kajiyama S, Hasegawa G, Asano M, Hosoda H, Fukui M, Nakamura N, Kitawaki J, Imai S, Nakano K, Ohta M, Adachi T, Obayashi H, Yoshikawa T: **Supplementation of hydrogen-rich water improves lipid and glucose metabolism in patients with type 2 diabetes or impaired glucose tolerance.** *Nutr Res* 2008. **28**:137-143.
47. Nakao A, Toyoda Y, Sharma P, Evans M, Guthrie N: **Effectiveness of Hydrogen Rich Water on Antioxidant Status on Subjects with Potential Metabolic Syndrome—An Open Label Pilot Study.** *J. Clin. Biochem. Nutr.* 2010. **46**:140-149.
48. Bolli, R: **Cardioprotective function of inducible nitric oxide synthase and role of nitric oxide in myocardial ischemia and preconditioning: an overview of a decade of research.** *J. Mol. Cell Cardiol.* 2001. **33**:1897-1918.

49. Isenberg JS: **Regulation of nitric oxide signaling by thrombospondin-1: implications for anti-angiogenic therapies.** *Nat Rev Cancer* 2009. **9**(3):2009.

50. Han W, Lijun W, Shaopeng C, Yu KN: **Exogenous Carbon Monoxide Protects the Bystander Chinese Hamster Ovary Cells in Mixed Coculture System After Alpha-Particle Irradiation.** *Carcinogenesis* 2010. **31**(2):275-280

51. Motterlini R, Mann BE, Foresti R: **Therapeutic applications of carbon monoxide-releasing molecules.** *Expert Opin Investig. Drugs* 2005. **14**:1305-1318.

52. Nakao A, Toyokawa H, Tsung A, Nalesnik MA, Stoltz DB, Kohmoto J, Ikeda A, Tomiyama K, Harada T, Takahashi T, Yang R, Fink MP, Morita K, Choi AM, Murase N: **Ex vivo application of carbon monoxide in university of wisconsin solution to prevent intestinal cold ischemia/reperfusion injury.** *Am. J. Transplant.* 2006. **6**:2243-2255.

53. Redl H, Bahrami S, Schlag G, Traber DL: **Clinical detection of LPS and animal models of endotoxemia.** *Immunobiology* 1993. **187**:330-345.

54. Klimisch HJ, Chevalier HJ, Harke HP, Dontenwill W: **Uptake of carbon monoxide in blood of miniature pigs and other mammals.** *Toxicology* 1975. **3**:301-310.

55. Kamoun P: **Endogenous Production of Hydrogen Sulfide in Mammals.** *Amino. Acids.* 2004. **26**:243-254.

56. Lowicka E, Beltowski J: **Hydrogen Sulfide (H_2S)—the Third Gas of Interest for Pharmacologist.** *Pharmacol. Rep.* 2007. **59**:4-24.

57. Abraïni JH, Gardette-Chauffour MC, Martinez E, Rostain JC, Lemaire C: **Psychophysiological Reactions in Humans During an Open Sea Dive to 500 m with a Hydrogen-Helium-Oxygen mixture.** *J. Appl. Physiol.* 1994. **76**:1113-1118.

58. Nakashima-Kamimura N, Mori T, Ohsawa I, Asoh S, Ohta S.: **Molecular hydrogen alleviates nephrotoxicity induced by an anti-cancer drug cisplatin without compromising anti-tumor activity in mice.** *Cancer Chemother Pharmacol* 2009. **64**:753-761.

59. Cardinal JS, Zhan J, Wang Y, Sugimoto R, Tsung A, McCurry KR, Billiar TR, Nakao A: **Oral hydrogen water prevents chronic allograft nephropathy in rats.** *Kidney Int.* 2009. **77**:101-109.

60. Cai J, Kang Z, Liu K, Liu W, Li R, Zhang JH, Luo X, Sun X: **Neuroprotective Effects of Hydrogen Saline in Neonatal Hypoxia-ischemia Rat Model.** *Brain Res* 2009. **1256**:129-137.

61. Pinsky DJ, Naka Y, Chowdhury NC, Liao H, Oz MC, Michler RE, Kubaszewski E, Malinski T, Stern DM: **The nitric oxide/cyclic GMP pathway in organ transplantation: critical role in successful lung preservation.** *Proc Natl Acad Sci* 1994. **91**:12086 – 12090.

62. Sun Q, Kang Z, Cai J, Liu W, Liu Y, Zhang JH, Denoble PJ, Tao H, Sun X: **Hydrogen-rich saline protects myocardium against ischemia/reperfusion injury in rats.** *Exp Biol Med* 2009. **234**:1212-1219.

63. Mao YF, Zheng XF, Cai JM, You XM, Deng XM, Zhang JH, Jiang L, Sun XJ: **Hydrogen-rich saline reduces lung injury induced by intestinal ischemia/reperfusion in rats.** *Biochem Biophys Res Commun* 2009. **381**:602-605.

64. Chen XL, Zhang Q, Zhao R, Medford RM: **Superoxide, H_2O_2 , and iron are required for TNF-alpha-induced MCP-1 gene expression in endothelial cells: role of Rac1 and NADPH oxidase.** *Am J Physiol Heart Circ Physiol* 2004. **286**:1001-1007.

65. Padmaja S, Huie RE: **The reaction of nitric oxide with organic peroxy radicals.** *Biochem. Biophys. Res. Commun.* 1993. **195**:539–544.

66. Kim YM, Bergonia H, Lancaster JR, Jr: **Nitrogen oxide-induced autoprotection in isolated rat hepatocytes.** *FEBS. Lett.* 1995. **374**:228–232.

67. Nunoshiba T, deRojas-Walker T, Wishnok JS, Tannenbaum SR, Demple B: **Activation by nitric oxide of an oxidative-stress response that defends *Escherichia coli* against activated macrophages.** *Proc. Natl. Acad. Sci.* 1993. **90**:9993–9997.

68. Ahluwalia A, Foster P, Scotland RS, McLean PG, Mathur A, Perretti M, Moncada S, Hobbs AJ: **Antiinflammatory activity of soluble guanylate cyclase: cGMP-dependent down-regulation of P-selectin expression and leukocyte recruitment.** *Proc. Natl. Acad. Sci.* 2004. **101**:1386–13891.

69. Nath KA, Balla J, Croatt AJ, Vercellotti GM: **Heme protein-mediated renal injury: a protective role for 21-aminosteroids in vitro and in vivo.** *Kidney Int.* 1995. **47**:592–602.

70. Kumar S, Bandyopadhyay U: **Free heme toxicity and its detoxification systems in human.** *Toxicol. Lett.* 2005. **157**(3):175–188.

71. Bilban M, Bach FH, Otterbein SL, Ifedigbo E, d'Avila JC, Esterbauer H, Chin BY, Usheva A, Robson SC, Wagner O, Otterbein LE: **Carbon monoxide orchestrates a protective response through PPARgamma.** *Immunity* 2006. **24**(5):601–610.

72. Taillé C, El-Benna J, Lanone S, Boczkowski J, Motterlini R: **Mitochondrial respiratory chain and NAD(P)H oxidase are targets for the antiproliferative effect of carbon monoxide in human airway smooth muscle.** *J. Biol. Chem.* 2005. **280**:25350–25360.

73. Zuckerbraun BS, Chin BY, Bilban M, d'Avila JC, Rao J, Billiar TR, Otterbein LE: **Carbon monoxide signals via inhibition of cytochrome c oxidase and generation of mitochondrial reactive oxygen species.** *FASEB J.* 2007. **21**:1099–1106.

74. Lee BS, Heo J, Kim YM, Shim SM, Pae HO, Kim YM, Chung HT: **Carbon monoxide mediates heme oxygenase 1 induction via Nrf2 activation in hepatoma cells.** *Biochem. Biophys. Res. Commun.* 2006. **343**:965–972.

75. Sawle P, Foresti R, Mann BE, Johnson TR, Green CJ, Motterlini R: **Carbon monoxide-releasing molecules (CO-RMs) attenuate the inflammatory response elicited by lipopolysaccharide in RAW264.7 murine macrophages.** *Br. J. Pharmacol.* 2005. **145**:800–810.

76. Hegazi RA, Rao KN, Mayle A, Sepulveda AR, Otterbein LE, Plevy SE: **Carbon monoxide ameliorates chronic murine colitis through a heme oxygenase 1-dependent pathway.** *J. Exp. Med.* 2005. **202**:1703–1713.

77. Whiteman M, Armstrong JS, Chu SH, Jia-Ling S, Wong BS, Cheung NS, Halliwell B, Moore PK: **The Novel Neuromodulator Hydrogen Sulfide: An Endogenous Peroxynitrite ‘scavenger’?** *J. Neurochem.* 2004. **90**:765–768.

78. Kimura Y, Kimura H: **Hydrogen Sulfide Protects Neurons from Oxidative Stress.** *FASEB J.* 2004. **18**:1165–1167.

79. Oh GS, Pae HO, Lee BS, Kim BN, Kim JM, Kim HR, Jeon SB, Jeon WK, Chae HJ, Chung HT: **Hydrogen Sulfide Inhibits Nitric Oxide Production and Nuclear Factor-kappaB via heme oxygenase-1 Expression in RAW264.7 Macrophages Stimulated with Lipopolysaccharide.** *Free Radic. Biol. Med.* 2006. **41**:106–119.

80. Qingyou Z, Junbao D, Weijin Z, Hui Y, Chaoshu T, Chunyu Z: **Impact of Hydrogen Sulfide on Carbon Monoxide/Heme Oxygenase Pathway in the Pathogenesis of Hypoxic Pulmonary Hypertension.** *Biochem. Biophys. Res. Commun.* 2004. **371**:30-37.
81. Laggner H, Muellner MK, Schreier S, Sturm B, Hermann M, Exner M, Gmeiner BM, Kapiotis S: **Hydrogen sulphide: a novel physiological inhibitor of LDL atherogenic modification by HOCl.** *Free Radic. Res.* 2007, **41**:741-747.
82. Sodha NR, Clements RT, Feng J, Liu Y, Bianchi C, Horvath EM, Szabo C, Sellke FW: **The Effects of Therapeutic Sulfide on Myocardial Apoptosis in Response to Ischemia-Reperfusion injury.** *Eur. J. Cardiothorac. Surg.* 2008. **33**:906-913.
83. Simon F, Giudici R, Duy CN, Schelzig H, Oter S, Gröger M, Wachter U, Vogt J, Speit G, Szabó C, Radermacher P, Calzia E: **Hemodynamic and Metabolic Effects of Hydrogen Sulfide During Porcine Ischemia/Reperfusion Injury.** *Shock* 2008. In press.
84. Blackstone E, Morrison M, Roth MB: **H₂S induces a suspended animation-like state in mice.** *Science* 2005. **308**:518.
85. Blackstone E, Roth MB: **Suspended animation-like state protects mice from lethal hypoxia.** *Shock* 2007. **27**:370-372.
86. Buchholz BM, Kaczorowski DJ, Sugimoto R, Yang R, Wang Y, Billiar TR, McCurry KR, Bauer AJ, Nakao A: **Hydrogen inhalation ameliorates oxidative stress in transplantation induced 170 intestinal graft injury.** *Am J Transplant* 2008. **8**:2015-24
87. Fujita K, Seike T, Yutsudo N, Ohno M, Yamada H, Yamaguchi H, Sakumi K, Yamakawa Y, Kido MA, Takaki A, Katafuchi T, Tanaka Y, Nakabeppu Y, Noda M: **Hydrogen in drinking water reduces dopaminergic neuronal loss in the 1-methyl-4- 173 phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease.** *PLoS One* 2009. **4**(9):e7247
88. Ad Hoc Committee on the Solar System Radiation Environment and NASA's Vision for Space Exploration: A Workshop Space Studies Board Division on Engineering and Physical Sciences: *Space Radiation Hazards and the Vision for Space Exploration.* Washington DC: The National Academies Press; 2006:7-37.
89. Strocchi A, Levitt MD: **Maintaining intestinal H₂ balance: credit the colonic bacteria.** *Gastroenterology* 1992. **102**:1424-1426.

TABLES AND CAPTIONS

TABLE 1. Cited Properties of H₂ as a Medical Gas with Suggested Chemical/Biological Mechanisms.

Biochemical Mechanism	Notes
radical scavenging antioxidant	<ul style="list-style-type: none"> selectively reduces hydroxyl radicals (•OH) and peroxynitrite (ONOO⁻) but did not eliminate O₂⁻ or H₂O₂ when tested in <i>in vitro</i> [42]. does not decrease the steady-state levels of nitric oxide (NO) [42] which may be beneficial as endogenous NO signaling pathways modulate pulmonary vascular tone and leukocyte/endothelial interactions [61]. increases antioxidant enzymes such as catalase, superoxide dismutase or heme oxygenase-1 [45,46].
anti-apoptotic	<ul style="list-style-type: none"> postulated to inhibit caspase-3 activation [62].
anti-inflammatory	<ul style="list-style-type: none"> down-regulation of pro-inflammatory cytokines, such as interleukin (IL)-1 β, IL-6, chemokine (CC motif) ligand 2 and tumor necrosis factor-α (TNF-α) [63,64].

TABLE 2. Cited Properties of NO as a Medical Gas with Suggested Chemical/Biological Mechanisms.

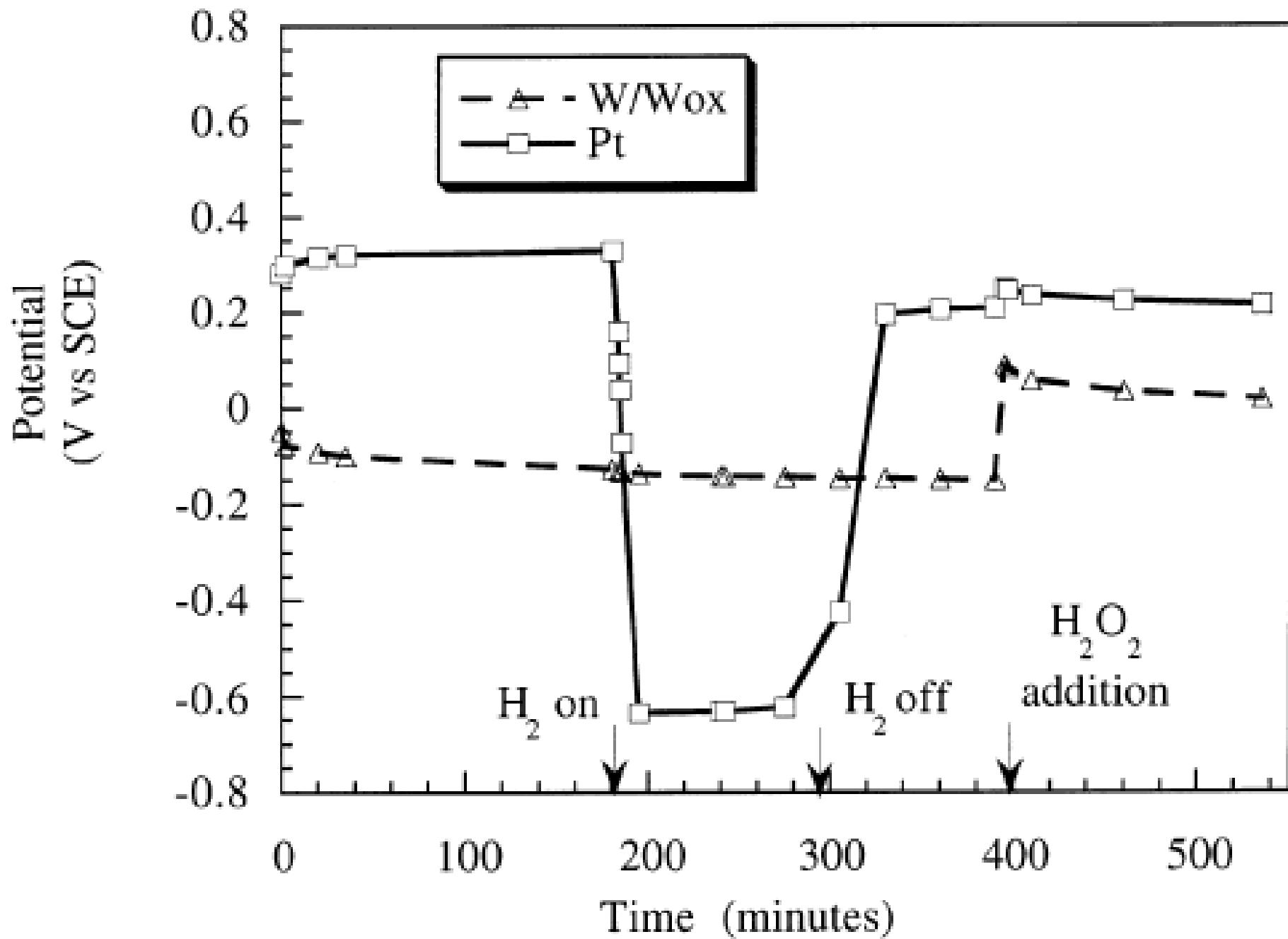
Biochemical Mechanism	Notes
radical scavenging antioxidant	<ul style="list-style-type: none"> NO reacts with peroxy and oxy radicals generated during the process of lipid peroxidation. The reactions between NO and these ROS can terminate lipid peroxidation and protect tissues from ROS-induced injuries [65]. induces the rate-limiting antioxidant enzyme, heme oxygenase (HO)-1 thus imparting resistance to H₂O₂ induced cell death [66]. in bacteria, activates the redox-sensitive transcriptional regulator protein (oxyR), resulting in the subsequent expression of protein protective against ROS [67].
anti-inflammatory	<ul style="list-style-type: none"> inhibiting P-selectin expression and leukocyte recruitment [68].
decreased radiosensitivity	<ul style="list-style-type: none"> vasodilator through relaxation of vascular tone by stimulating soluble guanylate cyclase (sGC) and increased cGMP content in vascular smooth muscle cells [22].

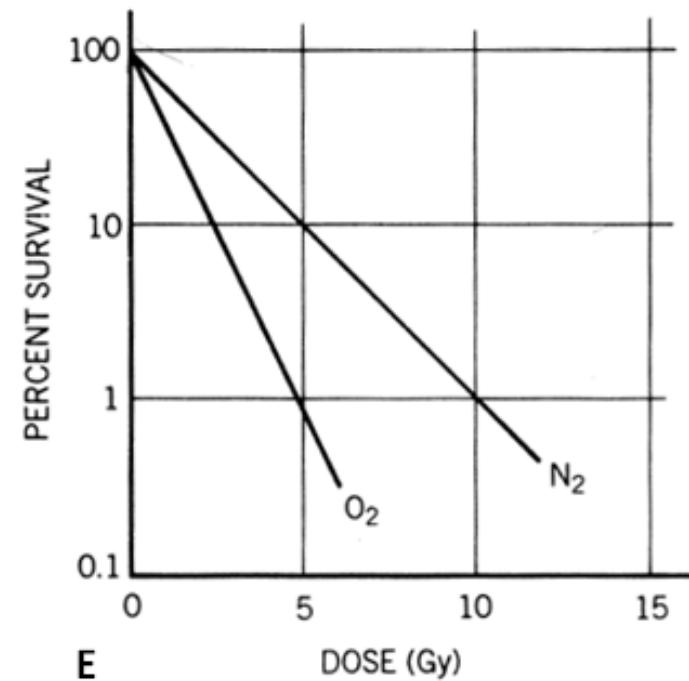
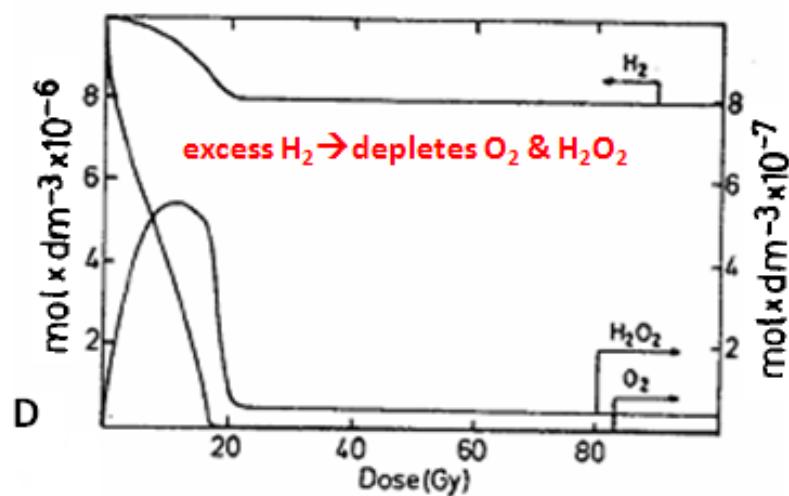
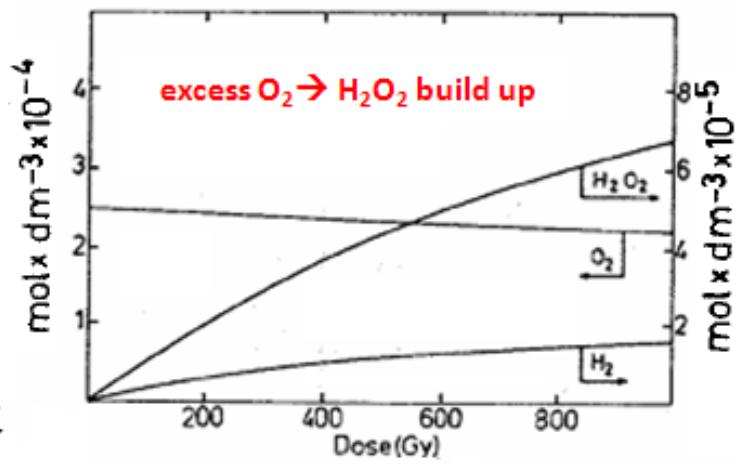
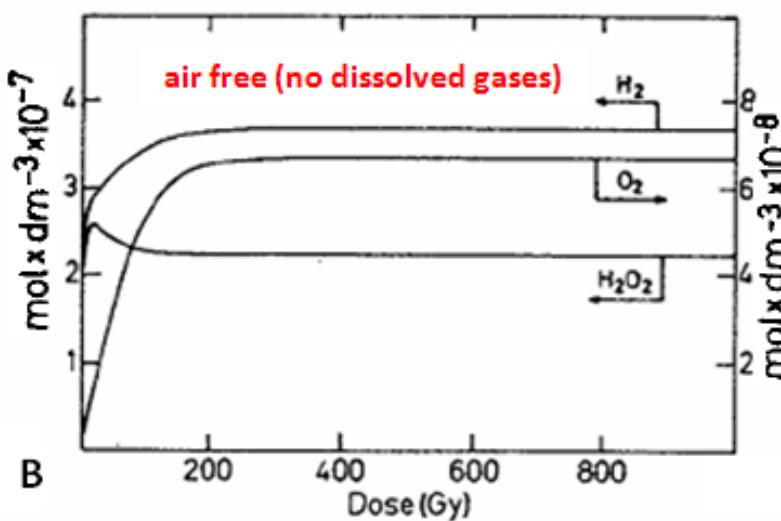
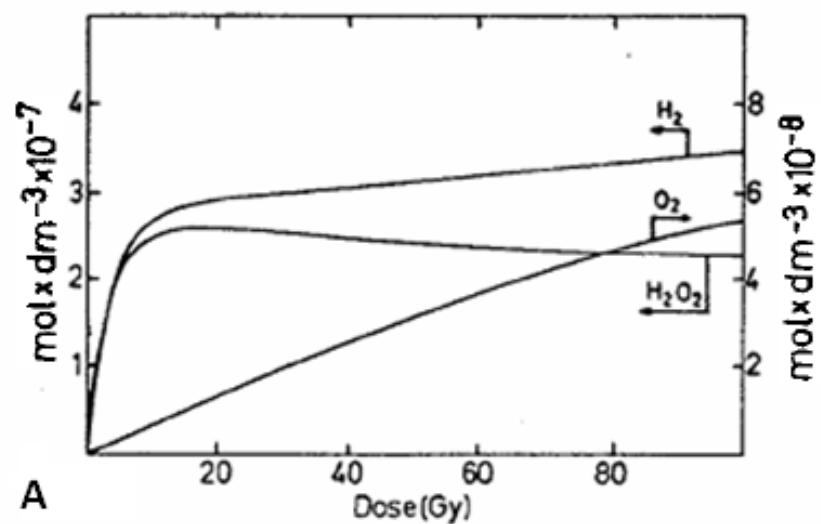
TABLE 3. Cited Properties of CO as a Medical Gas with Suggested Chemical/Biological Mechanisms.

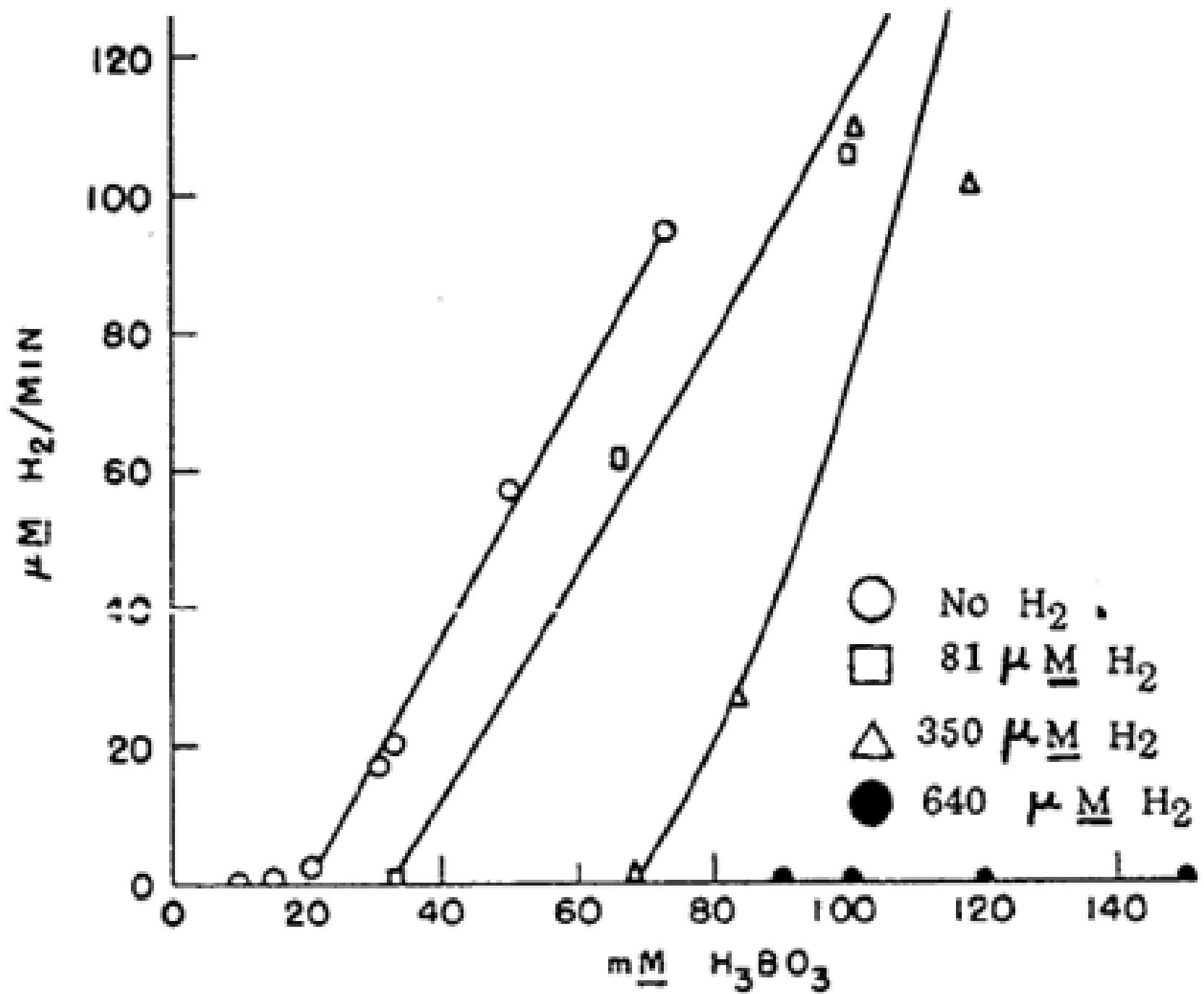
Biochemical Mechanism	Notes
radical scavenging antioxidant	<ul style="list-style-type: none"> binds to the heme moiety of mitochondrial cytochrome <i>c</i> oxidase. By binding to the heme, CO may prevent degradation of heme proteins which induce tissue injury by rapidly promoting peroxidation of the lipid membranes of cells [69, 70]. reduces mitochondria-derived ROS thus resulting in lower levels of ROS generation in which an adaptive cellular response is triggered leading to cell survival rather than cell death [71-73]. can induce HO-1 in cells to protect against injury [74-76]. Thus, detrimental excess of heme can be immediately removed by HO-1 enzymatic activity induced by CO.
decrease radiosensitivity	<ul style="list-style-type: none"> impedes O₂ transport as it binds to hemoglobin with an affinity 240 times higher than that of O₂.

TABLE 4. Cited Properties of H₂S as a Medical Gas with Suggested Chemical/Biological Mechanisms.

Biochemical Mechanism	Notes
radical scavenging antioxidant	<ul style="list-style-type: none"> antioxidant inhibitor of peroxynitrite-mediated processes via activation of N-methyl-D-aspartate (NMDA) receptors [77]. shield cultured neurons from oxidative damage by increasing levels of glutathione [78]. induce upregulation of HO-1, anti-inflammatory and cytoprotective genes [79, 80]. inhibits myeloperoxidase and destroys H₂O₂ [81].
anti-apoptotic	<ul style="list-style-type: none"> reduces IR induced apoptosis via reduction of cleaved caspase-3 and cleaved poly (ADP-ribose) polymerase (PARP) [82].
anti-inflammatory	<ul style="list-style-type: none"> inhibit leukocyte adherence in the rat mesenteric microcirculation during vascular inflammation [37].
decrease radiosensitivity	<ul style="list-style-type: none"> vasorelaxtion and vasodilation of isolated blood vessels via vascular smooth muscle K_{ATP} channel-mediated hyperpolarization [37, 22]. transiently and reversibly inhibiting mitochondrial respiration [37].
metabolic alteration	<ul style="list-style-type: none"> produces a “suspended animation-like” metabolic status with hypothermia and reduced oxygen demand in pigs (who received it intravenously) [83]. and mice (who received hydrogen sulfide via inhalation) [84, 85].







25 Gy



25 Gy + CD47 morpholino



